Remarks

Claims 1-11 and 61-62 are pending in this application. New claims 61-62 are added to recite free thalidomide and thalidomide salt or solvate, respectively. Support for these claims can be found, for example, on page 14, lines 15-17 of the specification. No new matter has been introduced.

Applicants respectfully submit that the pending claims are allowable for the following reasons.

On pages 2-5 of the Office Action, the rejection of claims 1-11 as allegedly obvious over Marx *et al.*, *Proc. Am. Soc. Clin. Oncology* 18: 454a (1999) ("Marx"), in view of Pitot *et al.*, *Journal of Clinical Oncology* 15(8): 2910-2919 (1997) ("Pitot") and U.S. Patent No. 5,622,959 to Priel *et al.* ("the '959 patent") is maintained. In particular, it is contended that because Marx allegedly discloses an anti-angiogenic effect of thalidomide, and Pitot and the '959 patent allegedly disclose antitumor activities of CPT-11 and CPT, respectively, the claimed invention is obvious. Applicants respectfully traverse this rejection.

In response to Applicants' submission that no *prima facie* case of obviousness can be established by the combination of Marx, Pitot and the '959 patent because there would have been no motivation to combine the cited references, the Examiner contends that "use of materials in combination, each of which is known to function for an intended purpose, is generally held to be prima facie obvious as the idea of combining them flows logically from their having been individually taught in the prior art." (Office Action, page 4). Applicants respectfully disagree.

It appears that the passage on which the Examiner relies is taken directly from *In re Kerkhoven,* 626 F.2d 848, 205 U.S.P.Q. 1069 (C.C.P.A. 1980). However, in *Kerkhoven*, the applicants claimed a process of making a detergent composition using two conventional detergents disclosed in the prior art. In contrast, the claimed invention is directed, in part, to the combination of two therapeutic agents. Combining two drugs for the treatment of a disorder in a human being is not analogous to combining detergents. For example, unfavorable drug-drug interactions are well known to those skilled in the art, and such interactions are not often predictable. By applying *Kerkhoven* to this case, the Examiner is oversimplifying the drug discovery process.

In this regard, Applicants previously noted that since thalidomide was not an approved anti-cancer drug at the time of the invention, and since there were

numerous other approved anti-cancer available at the time of the invention, those of ordinary skill in the art would not have been motivated to use thalidomide in combination with any other agent, much less a topoisomerase inhibitor. None of the references cited by the Examiner provide any suggestion or motivation for the combination of thalidomide and a topoisomerase inhibitor. This is all the more evident in view of the fact that topoisomerase inhibitors were known to be associated with various side effects such as gastrointestinal toxicities. (*See*, *e.g.*, Hecht, Exhibit B to Applicants' Response of June 24, 2005). For at least this reason, Applicants respectfully submit that no *prima facie* case of obviousness has been established by the references cited by the Examiner, and thus, request that the rejection of the claims be withdrawn.

More important, even assuming, *arguendo*, that a *prima facie* case of obviousness can somehow be established by the cited references, Applicants point out that any presumption of obviousness is rebutted by the unexpected results provided by the claimed invention. This is because, as disclosed in the specification, the claimed invention provides an unexpected synergy between thalidomide and a topoisomerase inhibitor (*e.g.*, irinotecan). The specification discloses that when thalidomide is co-administered with irinotecan to patients with metastatic colorectal cancer, a remarkable absence of gastrointestinal toxicity typically associated with irinotecan is observed. (The specification, page 31, line 24 - page 32, line 21).

Despite this fact, the Examiner maintains his contention that "the features upon which applicant relies (*i.e.*, co-administration of thalidomide and irinotecan to patients with colorectal cancer) are not recited" in the pending claims. (Office Action, page 4). In particular, the Examiner alleges that: 1) the present disclosure does not support that a synergistic effect is observed when any topoisomerase inhibitor is administered in combination with thalidomide; and 2) the disclosure does not support such a synergistic effect in the treatment of cancer broadly. (*Id.*) Applicants respectfully disagree.

First, to further evidence the patentability of the claimed invention, Applicants submit herewith a copy of *BioWorld Today*, November 4, 2005, page 2 (" the BioWorld article"). As the Examiner will see, the phase II clinical trial results of the combination of thalidomide and topotecan in the treatment of epithelial ovarian cancer are reported in the BioWorld article. It is reported that the combination of thalidomide and topotecan has an improved efficacy and safety in the treatment of

epithelial ovarian cancer as compared with topotecan alone. These results clearly show that combination of thalidomide and a topoisomerase inhibitor other than irinotecan is synergistically effective in the treatment of cancer other than colorectal cancer. Thus, Applicants respectfully point out that these results, along with the unexpected results presented in the current specification, are sufficient to rebut any presumption of obviousness[1] in connection with the whole scope of the claims.

To summarize, Applicants submitted various references which demonstrate that various topoisomerase inhibitors can be used for the treatment of cancer. (*See, e.g.*, Abstracts of Sugiura *et al.*, *Gan To Kagaku Ryoho*, 19(13): 2140-5 (1992), Chau *et al.*, *Free Radic Biol Med.*, 24(4): 660-70 (1998), Paz-Ares *et al.*, *Brit. J. Cancer*, 78(10): 1329-36 (1998), and Hecht, *Oncology*, 12(8 Suppl. 6): 72-8 (1998) ("Hecht")[2], all of which were submitted in Applicants' Response filed June 24, 2005 (disclosing anticancer activity of topoisomerase inhibitors CPT-11, topotecan, IST-622, β-lapachone, GI-147211, and irinotecan)). A synergistic effect of thalidomide and irinotecan in the treatment of colorectal cancer has been provided in the specification. A synergistic effect of thalidomide and topotecan in the treatment of epithelial ovarian cancer has been provided in the BioWorld article. Those of ordinary skill in the art would have had no reason to believe that such a synergism would not extend to the combination of thalidomide and other topoisomerase inhibitors (in view of the fact that irinotecan and topotecan are members of the class "topoisomerase inhibitors"), or types of cancer other than colorectal cancer (in view of the fact that various topoisomerase inhibitors are known to be effective in treating various types of cancer).

The Examiner fails to provide evidence to show that why the submitted unexpected results cannot be extended to other claimed species or ranges. (*See, e.g.*,

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[1] Applicants again submit that no *prima facie* case of obviousness has been established by the references cited by the Examiner.

[2] The Examiner, noting the teaching of Hecht that irinotecan is generally associated with gastrointestinal toxicities, alleges that no "nexus or motivation as to why one of ordinary skill in the art would assume that gastrointestinal toxicities are associated with all topoisomerase inhibitors or all cancer types" exists. (Office Action, page 4). However, Applicants never submitted that gastrointestinal toxicities are associated with all topoisomerase inhibitors. Applicants did indeed submit that Hecht does show that gastrointestinal toxicities of irinotecan is associated with the treatment of various cancer types using irinotecan.

In re Cescon, 474 F.2d 1331, 1334 (C.C.P.A. 1973) (holding that unexpected results showing a claimed compound's use in benzene rebuts the presumption of obviousness of the claim that recites the use of the compound in an inert solvent or substrate because "no factual basis appears in the record for expecting the compound to behave differently in other environments.")). Applicants respectfully point out that no factual basis that evidences the synergistic effect between thalidomide and irinotecan/topotecan in the treatment of colorectal/ovarian cancer cannot be extended to other topoisomerase inhibitors or other types of cancer is provided by the Examiner. All that is provided in the Office Action is the Examiner's conclusory statement that the unexpected results presented in the specification "does not support" the synergistic effect between thalidomide and a topoisomerase inhibitor in the treatment of cancer. (*See* Office Action, page 4). Therefore, to the extent that the rejection of the claims is based on this unsupported conclusion, Applicants respectfully submit that the full scope of the claims is non-obvious in view of data presented in the specification and herewith. Consequently, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103 be withdrawn.

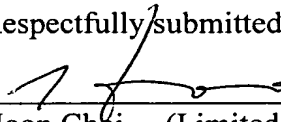
Conclusion

For at least the foregoing reasons, Applicants respectfully submit that all of the pending claims are allowable, and thus request that the rejection of the claims be withdrawn.

No fee is believed due for this submission. However, should any fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date January 17, 2006



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OTHER NEWS TO NOTE

• **Advancis Pharmaceutical Corp.**, of Germantown, Md., said it expects to start enrolling 600 patients later this month for a new Phase III trial of Amoxicillin Pulsys in adults and adolescents with pharyngitis/tonsillitis. The company concluded a pre-Phase III meeting with the FDA, and the regulatory strategy was acceptable to the agency. If the trial is successful, it will support a new drug application filing in late 2006. The product missed in two pivotal trials earlier this year, leading to a staff reduction and a dropped partnership. (See *BioWorld Today*, Sept. 16, 2005.)

• **Amazon Biotech Inc.**, of New York, is preparing an investigational new drug for a cancer drug candidate believed to be useful in early stage breast cancer. Some of the active ingredients have shown anticancer efficacy in in vitro studies. Amazon Biotech is a natural plant pharmaceutical company primarily developing immune modulator drugs.

• **American BioScience Inc.**, of Santa Monica, Calif., said clinical data of Abraxane showed high response rates in patients with non-small-cell lung cancer, metastatic malignant melanoma and head and neck cancer. Abraxane is an albumin-bound drug designed to work by using tumors' attraction to albumin to kill the cancer. The data were presented at the Chemotherapy Foundation Symposium XXIII in New York.

• **Angiotech Pharmaceuticals Inc.**, of Vancouver, British Columbia, entered a definitive agreement to acquire the Lifespan ePTFE vascular graft business in Laguna Hills, Calif. from **Edwards Lifesciences Corp.** for $14 million in cash. The agreement includes an arrangement in which Edwards will retain certain rights to distribute the existing Lifespan product line globally for up to five years, as well as become the exclusive distributor of Angiotech's Vascular Wrap paclitaxel-eluting mesh products in the European Union for up to three years following regulatory approval.

• **Bayer Pharmaceuticals Corp.**, of West Haven, Conn., and **Onyx Pharmaceuticals Inc.**, of Emeryville, Calif., said that Bernard Escudier provided an update on the Nexavar (sorafenib tosylate) Tablets Phase III trial in patients with advanced renal-cell carcinoma (RCC), or kidney cancer during the 13th European Cancer Conference (ECCO) in Paris. Escudier reported, based on an interim analysis, that there was an estimated 39 percent improvement in survival for patients receiving Nexavar vs. those receiving placebo (p=0.018, hazard ratio 0.72). More than 900 patients with advanced kidney cancer participated in the international Phase III study.

• **Celgene Corp.**, of Summit, N.J., said preliminary Phase II data comparing the efficacy and safety of the combination of thalidomide and topotecan vs. topotecan alone show that the addition of thalidomide could slow the growth of recurrent epithelial ovarian cancer in patients who had received prior treatments. Results showed that patients in the topotecan plus thalidomide arm reported an overall response rate of 50 percent, compared to 22 percent of patients receiving topotecan alone, and 32 percent of patients receiving both products showed a complete response vs. 16 percent of those in the topotecan arm. These data were presented at the XXIII Chemotherapy Foundation Symposium in New York.

• **Chromos Molecular Systems**, of Burnaby, British Columbia, said it entered a definitive agreement under which it will acquire **Targeted Molecules Corp.**, of San Diego, which is focused on the development of antibody product candidates for treatment of multiple sclerosis and acute thrombosis. Chromos also will complete a private placement to raise not less than $6 million, the proceeds of which will be used to finance operations. As a result of the acquisition, Chromos will gain two humanized monoclonal antibody product candidates, TMC-2003 for inflammatory diseases and NHAT for acute thrombosis. TMC has demonstrated efficacy of those candidates in preclinical proof of principle studies. TMC-2003 (to be re-designated CHR-1103) is a humanized monoclonal antibody directed to VLA-2, an integrin involved in maintenance of inflammation.

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